Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Bictegravir (BIC) (Last updated April 14, 2020; last reviewed April 14, 2020)

Formulations

Bictegravir is only available in a fixed-dose combination (FDC) tablet.

Fixed-Dose Combination Tablet:

- [Biktarvy] Bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg

When using FDC tablets, refer to other sections of the Drug Appendix for information about the individual components of the FDC. See also Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents.

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

[Biktarvy] Bictegravir/Emtricitabine/Tenofovir Alafenamide (TAF)

Child (Weighing <25 kg) Dose:

- There are currently no data available on the appropriate dose of Biktarvy in children aged <6 years and weighing <25 kg. Studies are currently being conducted to identify the appropriate dose for this age and weight group.

Child and Adolescent (Weighing ≥25 kg) and Adult Dose:

- One tablet once daily with or without food in antiretroviral therapy-naive patients. This dose of Biktarvy can also be used to replace the current antiretroviral (ARV) regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen for at least 3 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Biktarvy.

Selected Adverse Events

- Diarrhea, nausea, headache

Special Instructions

- Administer Biktarvy with or without food. See Drug Interactions below for guidance when administering Biktarvy with antacids or iron or calcium supplements.
- Screen patients for hepatitis B virus (HBV) infection before using emtricitabine (FTC) or TAF. Severe acute exacerbation of HBV can occur when discontinuing FTC or TAF; therefore, monitor hepatic function for several months after halting therapy with FTC or TAF.
- Biktarvy **is not recommended** for use with other ARV drugs.

Metabolism/Elimination

- Bictegravir is metabolized by cytochrome P450 3A4 and uridine diphosphate glucuronosyltransferase 1A1.

Biktarvy Dosing in Patients with Hepatic Impairment:

- Biktarvy **is not recommended** for use in patients with severe hepatic impairment.

Biktarvy Dosing in Patients with Renal Impairment:

- Biktarvy **is not recommended** for use in patients with estimated creatinine clearance <30 mL/min.

Drug Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker)

- *Metabolism:* Bictegravir (BIC) is a substrate of cytochrome P450 3A4 and uridine diphosphate glucuronosyltransferase (UGT) 1A1. Tenofovir alafenamide (TAF) is a substrate of P-glycoprotein and UGT1A1. Coadministration of the fixed-dose combination (FDC) tablet bictegravir/emtricitabine/

tenofovir alafenamide (BIC/FTC/TAF; Biktarvy) and rifampin is **contraindicated**.[1,2]

- *Renal effects:* BIC is an inhibitor of organic cation transporter 2 and multidrug and toxin extrusion protein 1, so it decreases tubular secretion of creatinine. This increases serum creatinine and reduces estimated glomerular filtration rate (eGFR) with no change in glomerular function. Drugs that decrease renal function could reduce clearance of FTC.
- *Absorption:* Administering BIC concurrently with antacids lowers the plasma concentrations of BIC. This is due to formation of complexes in the gastrointestinal tract, and not because of changes in gastric pH. Chelation by high concentrations of divalent cations, such as iron, decreases absorption of integrase strand transfer inhibitors (INSTIs), including elvitegravir and BIC. For this reason, Biktarvy should be administered at least 2 hours before or 6 hours after antacids and supplements or multivitamins that contain iron, calcium, aluminum, and/or magnesium when Biktarvy is given on an empty stomach. Biktarvy and antacids or supplements that contain calcium or iron can be taken together with food.

Major Toxicities

- *More common:* Diarrhea, nausea, headache. In two clinical trials, total bilirubin increased by up to 2.5 times the upper limit of normal in 12% of patients who received Biktarvy. In general, however, bilirubin increases were quite mild and did not lead to drug discontinuations in these trials.[2] BIC may cause an increase in creatine kinase concentration. Weight gain has been reported in adults who were receiving Biktarvy (see Table 15h).
- *Less common (more severe):* Severe immune reconstitution inflammatory syndrome may be more common with INSTIs than with other antiretroviral (ARV) agents.

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

BIC, which is only available as part of the FDC tablet BIC/FTC/TAF (Biktarvy), was approved by the Food and Drug Administration in 2018 for use in adults and in 2019 for use in children or adolescents weighing ≥25 kg. Biktarvy is approved for patients who have no ARV treatment history, and it can also be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen for at least 3 months with no history of treatment failure and no known mutations associated with resistance to the individual components of the FDC.[2]

Efficacy in Clinical Trials in Adults

In a short-term Phase 1 study, BIC monotherapy at doses of BIC 50 mg or BIC 100 mg was well tolerated. Three out of eight participants in both of these dosing groups achieved HIV RNA <50 copies/mL within 11 days.[3] The efficacy (defined as viral load suppression to HIV RNA <50 copies/mL) and safety (as measured by the incidence of study drug discontinuation or death) of Biktarvy were similar to the efficacy and safety of comparator regimens in two Phase 3 randomized trials in treatment-naive adults. Viral load suppression occurred in 89% of participants who received coformulated BIC 50 mg/FTC 200 mg/TAF 25 mg (n = 320) and in 93% of participants who received a regimen of dolutegravir (DTG) 50 mg plus FTC 200 mg plus TAF 25 mg (n = 325). Study drug discontinuation occurred in 1% of participants in both groups.

In a separate trial, viral load suppression occurred in 92% of participants who received BIC/FTC/TAF (n = 314) and in 93% of participants who received coformulated abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg (ABC/DTG/3TC) (n = 315). Study drug discontinuation was not reported for any of the participants who received BIC/FTC/TAF, though it did occur in 1% of participants who received ABC/DTG/3TC.[2,4]

Studies that randomized virologically suppressed patients who were on stable ARV regimens to either continue their current regimens or switch to coformulated BIC/FTC/TAF have shown that BIC/FTC/TAF has similar safety and efficacy to existing regimens. Viral load suppression occurred in 94% of participants who were randomized to switch to BIC/FTC/TAF (n = 282) and in 95% of participants who continued taking ABC/DTG/3TC (n = 281). Study drug discontinuation was reported in 2% of participants who received BIC/FTC/TAF and 1% of participants who received ABC/DTG/3TC. Ninety-two percent of participants who were randomized to switch to BIC/FTC/TAF (n = 290) achieved viral load suppression, while 89% of participants who continued receiving atazanavir-based or darunavir-based combination ARV regimens (n = 287) achieved viral load suppression. Study drug discontinuation occurred in 1% of participants in both of these groups.[2]

Pharmacokinetics

Pharmacokinetic (PK) studies of Biktarvy, which contains BIC 50 mg, have been performed in adults, adolescents aged 12 years to <18 years who weigh ≥35 kg, and children aged 6 years to <12 years who weigh ≥25 kg. These studies show a higher BIC C_{max} in the younger cohorts than in the older cohorts, perhaps because the administered dose is higher on a mg/kg basis (see Table A). The lower C_{trough} and higher C_{max} in the younger age/lower body weight cohorts suggests more rapid clearance in children and adolescents than in adults. Even though the mean serum trough concentrations in the child and adolescent cohorts are similar, there is a higher variability among the serum trough concentrations of the child cohort than among those of the adolescent or adult cohorts. This leads to a lower geometric mean ratio when C_{min} is compared to adult values, and the lower 90% confidence interval (CI) for the child cohort suggests that some patients have quite rapid clearance. This raises the concern that some of the patients in the youngest age/lowest body weight cohort may experience suboptimal trough concentrations, which may lead to less "pharmacologic forgiveness" in persons with lower adherence (see Table B below).[5]

Table A. Bictegravir Pharmacokinetics in Children, Adolescents, and Adults with HIV

PK Parameters	Children Aged 6 Years to <12 Years and Weighing ≥25 kg[6]	Adolescents Aged 12 Years to <18 Years and Weighing ≥35 kg[7]	Adults[2]
Dose (mg)	50	50	50
Dose for Lowest Weight in the Cohort (mg/kg)	2	1.43	1.25a
AUC_{tau} ng•h/mL Mean (CV%)	121,000 (36)	109,668 (31)	102,000 (26.9)
C_{max} ng/mL Mean (CV%)	11,000 (28)	8,087 (30)	6,150 (22.9)
C_{tau} ng/mL Mean (CV%)	2,370 (79)	2,327 (49)	2,610 (35)

[a] This dose was calculated using 40 kg as the lowest weight for adults.

Key: AUC_{tau} = area under the concentration time curve over the dosing interval; C_{max} = maximum serum concentration; C_{tau} = trough serum concentration at the end of the dosing interval; CV = coefficient of variation; PK = pharmacokinetic

Table B. Bictegravir Pharmacokinetics in Children and Adolescents with HIV

Cohort Characteristics	Dose (mg)	Dose for Lowest Weight in Cohort (mg/kg)	GMR% (90% CI) Compared to Adult Values[a]		
			AUC_{tau}	C_{max}	C_{tau}
Aged 6 Years to <12 Years and Weighing ≥25 kg[6]	50	2	116 (104–130)	177 (162–194)	78.3 (63.4–96.7)
Aged 12 Years to <18 Years and Weighing ≥35 kg[7]	50	1.43	107 (97–118)	130 (119–143)	86 (74–100)

[a] In this table, child and adolescent PK values are compared to the PK values of adults who received BIC 50 mg. The dose for the lowest weight in the adult cohort was 1.25 mg/kg; this was calculated using 40 kg as the lowest weight for adults.

Key: AUC_{tau} = area under the concentration time curve over the dosing interval; BIC = bictegravir; CI = confidence interval; C_{max} = maximum serum concentration; C_{tau} = trough serum concentration at the end of the dosing interval; GMR = geometric mean ratio; PK = pharmacokinetic

Use of Biktarvy in Adolescents Aged 12 Years to <18 Years

BIC 50 mg/FTC 200 mg/TAF 25 mg (Biktarvy) was administered to adolescents aged 12 years to <18 years who weighed ≥35 kg and who had had viral loads of <50 copies/mL for ≥6 months on their previous ARV regimens. The drug was well tolerated, and it was associated with a fall in eGFR that was similar to the one seen in adult studies. This decrease in eGFR was related to changes in tubular secretion of creatinine and was not a true change in glomerular function. While the area under the curve (AUC) and C_{max} for BIC were similar in adolescents and adults, the mean BIC trough concentration in adolescents aged 12 years to <18 years was 2,327 ng/mL (with a coefficient of variation [CV] of 49%); in adults, the mean BIC trough concentration was 2,610 ng/mL (CV 35%). The geometric mean ratio of the adolescent/adult trough concentration was 86% (90% CI, 74% to 100%). All 24 participants in the study had viral loads <50 copies/mL at Week 24.[7]

Use of Biktarvy in Children Aged 6 Years to <12 Years

BIC 50 mg/FTC 200 mg/TAF 25 mg was administered to children aged 6 years to <12 years who weighed ≥25 kg and who had had viral loads <50 copies/mL for ≥6 months on their current ARV regimens. Despite a high AUC and C_{max}, the drug combination was well tolerated, with a fall in eGFR similar to that seen in adult studies. There is higher variability among the serum trough concentrations of the child cohort than among those of the adolescent or adult cohorts, and a lower geometric mean ratio when C_{min} is compared to adult values (Table B), although population PK modeling suggests a C_{min} comparable to adult values.[8] All 50 participants in the study had viral loads <50 copies/mL at Week 12, and the 26 participants with data up to Week 24 likewise all had viral loads <50 copies/mL.[6]

The two studies described above were combined and carried to 48 weeks, at which time 74 of 75 participants had viral loads <50 copies/mL.[8]

References

1. Custodio JM, West SK, Collins S, et al. Pharmacokinetics of bictegravir administered twice daily in combination with rifampin. Presented at: Conference on Retroviruses and Opportunistic Infections. 2018. Boston, Massachussetts. Available at: http://www.croiconference.org/sessions/pharmacokinetics-bictegravir-administered-twice-daily-combination-rifampin.

2. Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210251s006lbl.pdf.

3. Gallant JE, Thompson M, DeJesus E, et al. Antiviral activity, safety, and pharmacokinetics of bictegravir as 10-day

monotherapy in HIV-1-infected adults. *J Acquir Immune Defic Syndr*. 2017;75(1):61-66. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28196003.

4. Gallant J, Lazzarin A, Mills A, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. *Lancet*. 2017;390(10107):2063-2072. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28867497.

5. Shuter J. Forgiveness of non-adherence to HIV-1 antiretroviral therapy. *J Antimicrob Chemother*. 2008;61(4):769-773. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18256112.

6. Cotton M, Liberty A, Rodriguez CA, et al. Pharmacokinetics, safety, and efficacy of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) single-tablet regimen in HIV-1-infected children (6 to < 12 years). Presented at: International AIDS Conference. 2018. Amsterdam, Netherlands. Available at: http://www.natap.org/2018/IAC/IAC_39.htm.

7. Gaur A, Rodriguez C, McGrath EJ, et al. Bictegravir/FTC/TAF single-tablet regimen in adolescents: week 24 results. Presented at: Conference on Retroviruses and Opportunistic Infections. 2018. Boston, Massachussetts. Available at: http://www.croiconference.org/sessions/bictegravirftctaf-single-tablet-regimen-adolescents-week-24-results.

8. Gaur A, Cotton M, Rodriguez C, et al. Bictegravir/FTC/TAF single-tablet regimen in adolescents & children: Week 48 results. Presented at: Conference on Retroviruses and Opportunistic Infections. 2019. Seattle, Washington. Available at: http://www.croiwebcasts.org/p/2019croi/46